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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,799	JOHANSEN, JACK T	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/27/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/27/2008 has been entered.

2. Applicant's amendment of claim 1 and the submission of new claim 28 in the paper filed on 06/27/2008 is acknowledged.

Claims 1-28 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 102(b)

3. The rejection of claims 1-8, 10, 12, 14, 16, 18, 19, 24, and 25 under 35 U.S.C. 102(b) as being anticipated by Bambara et al. (1975) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Claim Rejections Withdrawn - 35 USC § 103(a)

4. The rejection of claims 13 and 17 under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Lu et al. (1994) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

5. The rejection of claims 4, 8, and 15 under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Asteriadis et al. (1976) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

6. The rejection of claims 8 and 11 under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Jin-Yan et al. (WO9527718 published in 1995) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

7. The rejection of claims 9 under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Crane et al. (US Patent 5,092,992 issued 1992) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

8. The rejection of claims 20-23 and 26 under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Fruchtel et al. (1996) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

9. The rejection of claims 27 is 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) and further in view of Crane et al. (1992) and Asteriadis et al. (1976) is withdrawn. Applicant's arguments with respect to have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 102

10. Claims 1, 2, 6-8, 10-14, 16-21, 25, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Berglund et al. (United States Patent 6,090,288 issued July 18, 2000).

Regarding claims 1, 2, 10-13, 16, Berglund et al. teach methods of separating a target oligonucleotide from an impurity (see Abstract), in a mixture comprising said target oligonucleotide which is a synthetic phosphorothioate 25 mer oligonucleotide (see column 12 line 9) and the impurity, using a titratable anion exchange composition (see section *3. Chromatography (Nucleic Acid)* beginning in column 11 line 61), comprising the steps:

a) binding the target oligonucleotide to the titratable anion exchange composition comprising either the primary amine which is tris(hydroxymethyl)aminomethane (Tris-Ligand) or the tertiary amine which is trimethylamine (Q-ligand) at a first pH of pH 7.0; and

b) passing a solution through the titratable anion exchange composition with target oligonucleotide bound thereon, wherein the pH of said solution is increased over

time to a pH higher than the first pH by a linear pH gradient over time (see *Experiment 7.* beginning in column 14 line 2) from pH 7.0 (buffer A) to pH 9.0 (buffer F) thereby to elute the target oligonucleotide above pH 8.5 and thus inherently binds at pH 7.0 which is between pH 5 and 8, wherein said impurity which is unbound material of fraction A which elutes at a different pH of pH 7.0 (buffer A) than that of the target oligonucleotide.

Regarding claims 6-8, Berglund et al. teach where the anion exchange composition is conjugated to the support and where the support is synthetic polymer which is agarose (see section *1. Synthesis of Ion Exchanger* beginning in column 9 line 62).

Regarding claim 14, Berglund et al. teach increasing the solution from about pH 8 s this pH must be reached in going to pH 9.0 from pH 7.0 and where pH 9.0 is about pH 11.

Regarding claims 17 and 18, Berglund et al. teach that mixtures of oligonucleotides can be separated which contain shorter failure variants of the synthesized target oligonucleotides (see column 2 line 61-67).

Regarding claim 19, Berglund et al. teach inherent removal of the impurity which is the metal salt of sodium phosphate of Buffer A by replacing it with buffer F which has no sodium phosphate salt (see section *3. Chromatography (Nucleic Acid)* beginning in column 11 line 61).

Regarding claims 20 and 21, Berglund et al. teach where the target oligonucleotide is 5'-o-trityl protected (see column 15 line 1-29, *Experiment 9.*)

Regarding claim 25, Berglund et al. teach methods further comprising washing steps prior to elution (see section *3. Chromatography (Nucleic Acid)* beginning in column 11 line 61).

Regarding claim 28, Berglund et al. teach methods of separating a target oligonucleotide from an impurity (see Abstract), in a mixture comprising said target oligonucleotide which is a synthetic phosphorothioate 25 mer oligonucleotide (see column 12 line 9) and the impurity, using a titratable anion exchange composition (see section *3. Chromatography (Nucleic Acid)* beginning in column 11 line 61), comprising the steps:

a) binding the synthetic target oligonucleotide and impurities which are other bound oligonucleotides to the titratable anion exchange composition comprising either the primary amine which is tris(hydroxymethyl)aminomethane (Tris-Ligand) or the tertiary amine which is trimethylamine (Q-ligand) at a first pH of pH 7.0; and

b) passing a solution through the titratable anion exchange composition with synthetic target oligonucleotide bound thereon, wherein the pH of said solution is increased over time to a pH higher than the first pH by a linear pH gradient over time from pH 7.0 (buffer A) to pH 9.0 (buffer F) thereby to elute the synthetic target oligonucleotide above pH 8.5 and thus inherently binds at pH 7.0 which is between pH 5 and 8, wherein said impurity which is bound oligonucleotides elute at a lower pH of beginning at pH 8.5 than the synthetic target oligonucleotide which is bound up to pH 8.5 and elutes at higher pH thereafter (see *Experiment 7.* beginning in column 14 line 2).

Claim Rejections - 35 USC § 103

11. Claims 3-5 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claim 1 above, and further in view of Bambara et al. (1975, previously cited).

Berglund et al. teach as noted above.

Berglund et al. teach where the compositions comprise amines but do not specifically teach where the compositions comprise polyethyleneimine, potyimizadole, polyhistidine or polylysine.

Regarding claims 1 and 2, Bambara et al. teach a method of separating a target oligonucleotide, a primer, from an impurity, urea, in a mixture comprising said target oligonucleotide and said impurity of, using a titratable anion exchange composition, comprising the steps:

a) binding the primer target oligonucleotide to the titratable anion exchange composition of DEAE-cellulose, DEAE being a titratable tertiary amine and cellulose being the support to which the DEAE is conjugate;

b) passing a solution through said titratable anion exchange composition with target oligonucleotide bound thereon, wherein said solution increases in pH from 7.5 to 8.5 over time; and

c) eluting said target oligonucleotide, wherein said impurity elutes at a different pH than said target oligonucleotide (entire article, especially the first full paragraph in 2nd column on p. 4608).

It is noted DEAE-cellulose is N,N-diethylaminoethyl ether cellulose (CAS No. 9013-34-7).

In regards to claim 1, Bambara et al. do not specifically teach a solution which increase the PH over time to a pH higher than the first pH.

Regarding claims 3, Bambara et al. teach a method of separating a target oligonucleotide, a primer, from an impurity, "failed primers" using polyethyleneimine-cellulose by binding in a neutral solvent containing 1.2 M LiCl – 7 M urea solvent followed by pH increase to 8.5 (entire article, especially the first full paragraph in 2nd column on p. 4608 and Figure 9).

Regarding claims 4 and 5, Bambara et al. teach use of 0.2 M triethylamine bicarbonate buffer at pH 7.5 which is substantially free of metal salts followed by 0.2 M triethylamine bicarbonate buffer at pH 8.5 which has no increase in salt concentration.

As with Berglund et al. and regarding claim 19, Bambara et al. also teach a method wherein said impurity is the metal salt LiCl (see the 1st sentence of the first full paragraph in 2nd column on p. 4608).

Regarding claim 24, Bambara et al. inherently teach a method a method that concentrates the starting sample by teaching loading that starting sample onto a DEAE-cellulose in which the target primer becomes bound, that is, concentrated (see the 3rd sentence of the first full paragraph in 2nd column on p. 4608).

Berglund et al. teach the methods of separating a target oligonucleotide using the ompositions comprising an amine. Berglund et al. do not specifically teach where the compositions comprise polyethyleneimine.

Bambara et al. teach methods of separating a target oligonucleotide using the compositions comprising an amine and specifically teach where the compositions comprise polyethyleneimine. Because both Berglund et al. and Bambara et al. teach methods of separating a target oligonucleotide using the compositions comprising an amine, it would have been obvious to one skilled in the art to substitute an amine which is polyethyleneimine as taught by Bambara et al. for any of the amines taught by Berglund et al. in order to achieve the predictable result of the method of separating a target oligonucleotide using the compositions comprising an amine where the amine is polyethyleneimine.

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claims 1 and 8 above, and further in view of Crane et al. (1992, previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach polyethyleneimine-derivatized silica gel.

Regarding claim 9, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Berglund et al. by

using polyethyleneimine-derivatized silica gel as suggested by Crane et al. with a reasonable expectation of success. The motivation to do so is provided by Crane et al. who teach the usefulness of and polyethyleneimine-derivatized silica gel in chromatography and the teaching of Berglund et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

13. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claims 1 and 7 above, and further in view of Asteriadis et al. (1976, previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH.

Regarding claim 15, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Berglund et al. by using a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH as suggested by Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Asteriadis et al. who teach the usefulness of a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH for purification of oligonucleotides and the teaching of Berglund et al. for the separation of

oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

14. Claims 22, 23, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claims 1 above and further in view of Fruchtel et al. (1996).

Berglund et al. teach as noted above.

Berglund et al. teach a method wherein a target oligonucleotide is 5'-O-protected, is 5'-O-trityl protected, but do not specifically teach where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid.

Regarding claims 20 and 21, Fruchtel et al. where the target oligonucleotide is 5'-O-trityl protected (entire reference, especially p. 20 1st paragraph).

Regarding claims 22 and 23, Fruchtel et al. teach that acid condition cleave 5'-O-trityl protecting group including acetic acid (see 2nd sentence on page 20: " . . . the trityl anchoring bond can be cleaved by very weak acids such as acetic acid").

Regarding claim 26, Fruchtel et al. teach where the target oligonucleotide is is 5'-O-dimethoxy-trityl protected (entire reference, especially Scheme 41 on p 39 and footnote on page 17).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Berglund et al. where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting

group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; as suggested by Fruchtel et al. with a reasonable expectation of success. The motivation to do so is provided by Fruchtel et al. who teach the usefulness of a target oligonucleotide which is 5'-O-protected, which is 5'-O-trityl protected, where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; and the teaching of Berglund et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

15. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claim 1 above and further in view of Bambara et al. (1975, previously cited), Crane et al. (1992 previously cited), and Asteriadis et al. (1976 previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach a method wherein a titratable anion exchange composition comprises polyethyleneimine, polyimizadole, polyhistidine or polylysine conjugated to a synthetic polymer support; and the solutions comprises one or more specifically of NH_4HCO_3 and/or NH_4OH.

Regarding claim 27 in part that Bambara et al. teach a method wherein a solution increases from a pH of 7.5 which is about 8 to a pH of 8.5, which is about 11; teach

solutions substantially free of metal salts where the change in buffer does not substantially increase salt concentration over time; teach an polyethyleneimine conjugated to solid support; and teach an amine carbonate.

Regarding claim 27 in part, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Regarding claim 27 in part, Asteriadis et al. teach a method wherein a solution is relatively of relatively low salt concentration, that is substantially free of metal salts and other salts (entire reference, especially p. 65, 2nd paragraph, 2nd sentence).

Regarding claim 27 in part, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Berglund et al. by using an amine which is polyethyleneimine conjugated to solid support as taught by Bambara et al.; by using a polyethyleneimine-derivatized silica gel, a solution is relatively of relatively low salt concentration, and a solution of NH_4OH as suggested by Crane et al. and Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Crane et al. and Asteriadis et al. who teach the usefulness of a polyethyleneimine-derivatized silica gel, a solution is relatively of relatively low salt concentration, and a solution of NH_4OH and the teaching of Bambara et al. for the separation of oligonucleotides with an amine which is polyethyleneimine. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

16. No claim is free of the prior art

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
August 26, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637